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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RODNEY J. HO and CHE-CHUNG TSAI

Appeal 2011-003317
Application 10/757,775
Technology Center 1600

Before FRANCISCO C. PRATS, JEFFREY N. FREDMAN, and STEPHEN WALSH, Administrative Patent Judges.

FREDMAN, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a lipid-drug complex. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

Background

"A lipid-drug complex, such as a liposome, readily encapsulates drugs having low aqueous solubility within a neutral pH range" (Spec. 7, ll. 12-14). "The methods for targeting lymphoid tissue involve subcutaneous administration of lipid-drug complexes and lipid-biomolecule complexes" (Spec. 7, ll. 19-21).

The Claims

Claims 1-3, 5-9, and 15-17 are on appeal. Claims 1 and 6 are representative and read as follows:

> 1. A lipid-drug complex for subcutaneous administration comprising:
> at least one lipid molecule, and
> at least one drug molecule having low aqueous solubility within a neutral pH range; and
> wherein the at least one drug molecule substantially dissociates from the lipid-drug complex within a pH range from about pH 5.0 to about pH 5.5.
>
> 6. The lipid-drug complex of Claim 1, wherein the liposome is a unilamellar liposome.

The issues

A. The Examiner rejected claims 1-3, 5, 7-9, and 15-17 under 35 U.S.C. § 103(a) as obvious over Kirpotin[1] (Ans. 4-6).

B. The Examiner rejected claim 6 under 35 U.S.C. § 103(a) as obvious

[1] Dmitiri Kirpotin, US 6,110,491, issued Aug. 29, 2000.

over Kirpotin, Thibodeau,[2] and Konigsberg[3] (Ans. 6-7).

C. The Examiner rejected claims 1-3, 5-9, and 15-17 under 35 U.S.C. § 103(a) as obvious over Bergeron[4] and Kirpotin (Ans. 7-9).

A. 35 U.S.C. § 103(a) over Kirpotin

The Examiner finds that Kirpotin teaches "liposomes composed of the lipids egg phosphatidycholine (PC), cholesterol (CHOL) and teach lipid to drug ratio of 1 μm to 200 nm (example 1) which is 5:1" (Ans. 4). The Examiner finds that Kirpotin teaches "suitable compounds in the liposome complex preparation include low water solubility compounds preferably in the pH range of 3-9 such as HIV protease inhibitors including indinavir" (id.). The Examiner finds that "Kirpotin teaches that liposomes can be prepared in the desired size range, typically between 0.03-1 micron, preferably between 0.03 to 0.5 microns and further teaches that homogenization methods are also useful for down-sizing liposomes to sizes of 100 nm or less" (id.).

The Examiner finds that Kirpotin does "not explicitly teach that the drug substantially dissociates from the lipid-drug complex within a pH range of 5.0-5.5 . . . Regarding the claimed dissociation properties . . . the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art" (id. at 5).

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[2] Lise Thibodeau, Immunosome Technology to Improve Antigen Presentation for Efficient and Safe Viral Vaccines, 1 MOLECULAR ENGINEERING 275-293 (1991).
[3] Konigsberg et al., US 5,258,499, issued Nov. 2, 1993.
[4] Bergeron et al., US 5,773,027, issued Jun. 30, 1998.

Appellants contend that "it is nothing short of absurd for the Examiner to assert that a particular property is inherent in all or any particular lipid aggregates without some support, suggestion, or authority for the assertion" (App. Br. 4-5). Appellants contend that "M.P.E.P. § 2112 makes it very clear that the Examiner must show that Kirpotin's drug encapsulating liposomes are identical or nearly identical to the currently claimed lipid-drug complex" (id. at 6). Appellants contend that the "Examiner has not attempted to make such showing, providing a single sentence statement suggesting that, because Kirpotin's drug-encapsulating liposomes contain lipids, and encapsulate drugs, they are sufficiently 'identical' to allow for a rejection based on inherency" (id.).

Appellants contend that there "are many statements in Kirpotin and in the current application from which one of ordinary skill in chemistry or biochemistry would necessarily conclude that the rigid-lipid-bilayer liposomes created by Kirpotin's method are very different from the lipid-drug complex claimed in claim 1" (id.).

Appellants contend that "Kirpotin explicitly teaches that the precipitated drug within Kirpotin's drug encapsulating liposomes cannot dissociate from the liposomes in the pH range of about pH 5.0 to about pH 5.5 at which the drug dissociates from the currently claimed lipid-drug complex" (id. at 7).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the burden of showing whether Kirpotin's lipid-drug complex inherently satisfies the functional requirement of claim 1 that "at least one drug molecule substantially

dissociates from the lipid-drug complex within a pH range from about pH 5.0 to about pH 5.5" is properly placed on Appellants?

Findings of Fact

1. The Specification teaches that a "'complex' can mean any mixture or aggregation that results from the formation of any type of chemical binding/bonding reaction among the constituents or components of the complex" (Spec. 9, ll. 12-14).

2. The Specification teaches that a "'lipid-drug complex' can mean a complex in which at least one component is any form of a lipid molecule, and at least one component is any form of a pharmaceutical agent" (Spec. 9, ll. 17-19).

3. The Specification teaches that "lipid-drug complexes of the present invention may adopt various types of configurations, including the spherical shape of liposomes . . . A liposome forms generally as a vesicle comprising a lipid bilayer membrane with an aqueous internal space" (Spec. 9, ll. 23-26).

4. The Specification teaches that the

> present invention does not depend on a particular chemical or biochemical mechanisms by which the inventive lipid-drug formulations are obtained, or by which the drug is released to target lymphoid cells. However, it is thought that the complementary structure of the drug, e.g., indinavir (as it assumes lipophilic form at pH 7.4) intercalates within the lipid bilayer. . . . Titration back to a neutral pH range decreases the aqueous solubility of the drug and increases its lipophilicity, and results in the association between the drug and the lipid bilayer of the liposome. It is thought that endocytosis of the liposomes by cells results in the sequestration within the intracellular acidic vesicles, and that

> the acidic pH of the vesicles increases the aqueous solubility of the drug, resulting in its release from the liposome into the cell.

(Spec. 11, ll. 15-29.)

5. The Specification teaches that "phosphatidylcholine and cholesterol at 3:1 molar ratio are employed. However, any suitable molar ratio of a non-steroidal, lipid-steroidal lipid (e.g., cholesterol) mixture can optionally be employed that promotes the stability of a particular lipid-drug complex during storage and/or delivery to a mammalian subject" (Spec. 13, l. 31 to 14, l. 2).

6. The Specification teaches that "[m]ixing the drug and lipids can be by any useful known technique, for example, by . . . extrusion . . . homogenization . . . The drug and lipid are mixed at a lipid-to-drug molar ratio of about 3: 1 to about 100: 1 or higher . . . and most preferably about 5: 1 to about 7: 1" (Spec. 14, ll. 3-8).

7. Kirpotin teaches "a novel liposome composition containing liposomes suspended in a bulk-phase aqueous medium, and an ionizable compound contained within the liposomes in the form of a stable precipitate" (Kirpotin, col. 4, ll. 55-58).

8. Kirpotin teaches that "[e]xample 1 describes preparation liposomes composed of the lipids egg phosphatidycholine (PC), cholesterol (CHOL) and polyethylene glycol derivatized distearolphosphatidyl ethanolamine (PEG-DSPE). The lipids, at a molar ratio of 10:5:1 PC:CHOL:PEG-DSPE were dissolved" (Kirpotin, col. 9, ll. 59-63).

9. Kirpotin teaches that suitable compounds include "HIV protease inhibitors: indinavir, ritonavir, and saquinavir" (Kirpotin, col. 8, ll. 32-33).

10. Kirpotin teaches that the

> internal pH of the liposomes in the composition is preferably at or near the minimum-solubility pH of the precipitated compound, or at a lower pH of 4 to 5.5 or an upper pH of 8.5 to 10. As indicated above, the bulk phase pH may be adjusted to the internal pH, eliminating any transmembrane pH in the composition, particularly if necessary to bring the bulk phase pH within the range pH 6-8 suitable for parenteral use.

(Kirpotin, col. 8, ll. 34-41.)

11. Kirpotin teaches that "[l]iposomes are then sized to the desired size range, typically between 0.03-1 micron, preferably between 0.03 to 0.5 microns" (Kirpotin, col. 10, ll. 1-3).

12. Kirpotin teaches that a "standard sizing method involves extruding an aqueous suspension of the liposomes through a series of polycarbonate membranes having a selected uniform pore size in the range of 0.03 to 0.2 micron . . . Homogenization methods are also useful for down-sizing liposomes to sizes of 100 nm or less" (Kirpotin, col. 10, ll. 3-12).

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." Id. at 417.

"Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product." In re Best, 562 F.2d 1252, 1255 (CCPA 1977).

Analysis

Claim 1, read in light of the Specification (FF 1-2), simply requires a complex of a lipid molecule and a drug molecule having low aqueous solubility within a neutral pH range such as indinavir (FF 4), where the complex also satisfies the wherein clause.

Kirpotin teaches formation of a complex of a lipid molecule and indinavir (FF 7-9). It is undisputed that Kirpotin is silent as to the inherency of the functional limitation of whether "the at least one drug molecule substantially dissociates from the lipid-drug complex within a pH range from about pH 5.0 to about pH 5.5" (Claim 1).

> [W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on....
> Whether the rejection is based on "inherency" under 35 U.S.C. § 102, on "prima facie obviousness" under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

In re Best, 562 F.2d at 1254-55.

We agree with the Examiner, who expressly relied upon the Best doctrine, that Appellants are better placed than the USPTO to demonstrate whether when Kirpotin's liposomes formed with indinavir are placed at a pH of 5.0 to 5.5, the indinavir dissociates from the liposome, satisfying the functional limitation of claim 1 (Ans. 5).

Appellants contend that "it is nothing short of absurd for the Examiner to assert that a particular property is inherent in all or any particular lipid aggregates without some support, suggestion, or authority for the assertion" (App. Br. 4-5). Appellants contend that "M.P.E.P. § 2112 makes it very clear that the Examiner must show that Kirpotin's drug encapsulating liposomes are identical or nearly identical to the currently claimed lipid-drug complex" (id. at 6).

We are not persuaded. There can be no reasonable dispute that Kirpotin suggests a lipid-drug complex in the form of a liposome composed of a phospholipid and cholesterol (FF 7-8) with a drug, indinavir, which has low aqueous solubility within a neutral pH range (FF 9). The Examiner has shown that Kirpotin's lipid-drug complex satisfies the structural elements of claim 1. Appellants' claim 1 does not require any specific lipids, specific forms such as liposomes, specific drugs nor does claim 1 require any particular process for making the lipid-drug complex (see Claim 1).

Appellants contend that there "are many statements in Kirpotin and in the current application from which one of ordinary skill in chemistry or biochemistry would necessarily conclude that the rigid-lipid-bilayer liposomes created by Kirpotin's method are very different from the lipid-drug complex claimed in claim 1" (App. Br. 6). Appellants contend that as

> discussed in the Appeal Brief, the currently claimed lipid-drug complex is prepared by a different method than Kirpotin's disclosed drug-encapsulating liposomes. Those familiar with chemistry, biochemistry, and molecular biology well understand that the structure and contents of a complex molecular aggregate containing thousands, hundreds of thousands, or millions of molecules may, in fact, be determined by the procedure used to prepare the molecular aggregate

(Reply Br. 2).

We are not persuaded. There are no statements in claim 1 which exclude the liposomes of Kirpotin from the lipid-drug complex. Indeed, Appellants' Specification teaches that a "'lipid-drug complex' can mean a complex in which at least one component is any form of a lipid molecule, and at least one component is any form of a pharmaceutical agent" (Spec. 9, ll. 17-19; FF 2). Even reading claim 1 in light of the Specification, the Specification's broad definition reasonably encompasses the liposomes of Kirpotin (FF 1-3).

To the extent that Appellants rely upon their specific methods of liposome synthesis, these limitations are not found in claim 1. "[L]imitations are not to be read into the claims from the specification." In re Van Geuns, 988 F.2d 1181, 1184 (Fed. Cir. 1993). Not only does claim 1 fail to incorporate any limitations on the mode of synthesis of the lipid drug complex, but Appellants own Specification states that "[m]ixing the drug and lipids can be by any useful known technique, for example, by . . . extrusion . . . homogenization" (Spec. 14, ll. 3-8; FF 6).

Appellants contend that "Kirpotin explicitly teaches that the precipitated drug within Kirpotin's drug encapsulating liposomes cannot dissociate from the liposomes in the pH range of about pH 5.0 to about pH 5.5 at which the drug dissociates from the currently claimed lipid-drug complex" (App. Br. 7).

We are not persuaded. Appellants infer that since the internal pH in Kirpotin's liposomes is low, the drug is "unavailable for release or dissociation from the liposomes at the very pH range of 5.0 to 5.5" (App. Br. 7). However, this simply represents attorney argument, since Appellants provide no evidence to show what result would obtain upon placement of Kirpotin's liposomes with indinavir into a pH range of 5.0 to 5.5. See In re Pearson, 494 F.2d 1399, 1405 (CCPA 1974) ("Attorney's argument in a brief cannot take the place of evidence.").

Conclusion of Law

The evidence of record supports the Examiner's conclusion that the burden of showing whether Kirpotin's lipid-drug complex inherently satisfies the functional requirement of claim 1 that "at least one drug molecule substantially dissociates from the lipid-drug complex within a pH range from about pH 5.0 to about pH 5.5" is properly placed on Appellants.

B. 35 U.S.C. § 103(a) over Kirpotin, Thibodeau, and Konigsberg

The Examiner finds, regarding claim 6, that "Kirpotin does not teach the liposome to be unilamellar" (Ans. 6). The Examiner finds it obvious "to make a lipid drug complex where the liposome is unilamellar because . . . Thibodeau teach the preparation of unilamellar liposomes in antigen

delivery and Konigsberg et al. teach that unilamellar liposomal liposomes have been shown to be useful in targeting solid tumors and to have greater circulation times than other vehicles" (Ans. 7).

Appellants contend that the "rejection of claim 6 depends primarily on Kirpotin. As discussed under Issue 1, Kirpotin does not teach, mention, or suggest that for which it is cited" (App. Br. 8). Appellants contend that

> Neither Thibodeau nor Konigsberg teaches, mentions, or even remotely suggests a lipid aggregate or liposome that releases a complex drug within the pH range of pH 5.0 to pH 5.5. Clearly, the Examiner's conclusory statement that release of drug in that pH range is somehow inherent to all lipid aggregates, regardless of how they are prepared, cannot serve as the basis for an obviousness-type rejection

(App. Br. 9).

We find that the Examiner has the better position. The Examiner relies upon specific evidence and reasoning in the prior art to suggest modification of Kirpotin's liposomes to form unilamellar liposomes (see Ans. 6-7). We adopt the fact finding and analysis of the Examiner as our own. Appellants argue the underlying obviousness rejection over Kirpotin, but Appellants do not identify any material defect in the Examiner's reasoning for combining Thibodeau and Konigsberg with Kirpotin. Since Appellants only argue the underlying rejection over Kirpotin which we affirmed above, we affirm this rejection for the reasons stated by the Examiner.

C. 35 U.S.C. § 103(a) over Bergeron and Kirpotin

The Examiner finds that Bergeron teaches liposomes comprising "a

lipid component comprising a mixture of diacylphosphatidylcholine and diacylphosphatidyl glycerol and ii) a therapeutic amount of an entrapped drug such as saquinavir effective against said viral disease" (Ans. 7). The Examiner finds that Bergeron "does not teach indinavir (elected species) as the drug and phosphatidyl choline (elected species) as the lipid in the lipid-drug complex" (Ans. 8). The Examiner finds that "Kirpotin teach the same components of the lipid-drug complex, the drug indinavir can be entrapped in a liposome as claimed in the instant application. The reference also teaches that the lipid-drug complex can be parenterally administered and subcutaneous administration is a type of parenteral administration" (id.). The Examiner finds it obvious over Bergeron and Kirpotin "to formulate a lipid drug complex comprising indinavir as the drug and phosphatidylcholine as the lipid in the lipid-drug complex" (id.).

Appellants contend that "Bergeron's drug-encapsulating liposomes are reported by Bergeron as having diameters of between 100 nm and 300 nm, in contrast to the 50 nm to 80 nm diameters of the currently claimed lipid-drug complex, and are prepared by methods that differ substantially from the methods employed to create the lipid-drug complex of the present invention" (App. Br. 9-10). Appellants contend that the "Examiner cannot simply shift the burden to Applicants by citing references that do not teach, mention, or even remotely suggest lipid-drug complexes with the claimed drug-releasing property and that disclose drug-encapsulating liposomes prepared by different methods than those used to prepare the currently claimed lipid-drug complex" (id. at 10).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the burden of showing whether Bergeron and Kirpotin's lipid-drug complex inherently satisfies the functional requirement of claim 1 that "at least one drug molecule substantially dissociates from the lipid-drug complex within a pH range from about pH 5.0 to about pH 5.5" is properly placed on Appellants?

Findings of Fact

13. Bergeron teaches "treatment of viral diseases comprising the administration of antiviral agents encapsulated in liposomes" (Bergeron, col. 2, ll. 34-36).

14. Bergeron teaches "liposomes composed of i) a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol" (Bergeron, col. 3, ll. 58-60).

15. Bergeron teaches "[l]iposomes generated by this technique are unilamellar or plurilamellar and generally range in size from 0.2 to 5 μm" (Bergeron, col. 4, ll. 53-54).

16. Bergeron teaches that any "inhibitor of viral DNA and/or RNA synthesis and/or HIV protease is under the scope of this invention. Included in this class are antiviral agents such as . . . saquinavir" (Bergeron, col. 4, ll. 58-62).

Analysis

Bergeron teaches a lipid-drug complex composed of a lipid molecule and a drug having low aqueous solubility within a neutral pH range (FF 1-6, 11-16). Bergeron is silent as to the inherency of the functional limitation of whether "the at least one drug molecule substantially dissociates from the

lipid-drug complex within a pH range from about pH 5.0 to about pH 5.5" (Claim 1).

While the Examiner limits the analysis to the elected species (see, e.g., Non-Final Rejection 1/25/2008), we find that Bergeron teaches liposomes which satisfy the structural requirements of claim 1. We agree with the Examiner that it would have been obvious to incorporate the elected lipid species of phosphatidyl choline and the elected antiviral drug indinavir taught by Kirpotin into the liposomes of Bergeron, since "Kirpotin teaches the equivalence of indinavir and saquinavir . . . Kirpotin teaches lipid drug complexes with the lipids including phosphatidylcholine" (Ans. 8).

We also agree with the Examiner that the Best doctrine is applicable here (see Ans. 9) since Appellants are better situated to demonstrate whether Bergeron's liposomes with saquinavir would inherently result in a liposome in which "at least one drug molecule substantially dissociates from the lipid-drug complex within a pH range from about pH 5.0 to about pH 5.5" as required by claim 1.

Appellants contend that "Bergeron's drug-encapsulating liposomes are reported by Bergeron as having diameters of between 100 nm and 300 nm, in contrast to the 50 nm to 80 nm diameters of the currently claimed lipid-drug complex, and are prepared by methods that differ substantially from the methods employed to create the lipid-drug complex of the present invention" (App. Br. 9-10).

We are not persuaded. Appellants' own claim 16 permits the lipid-drug complex to range from "about 30 to about 150 nanometers in diameter" (Claim 16). There is no limitation in claim 1 requiring a range of 50 nm to

80 nm. To the extent that this represents a separate argument for the patentability of claim 17, which does require that "the lipid-drug complex is about 50 to about 80 nanometers in diameter," we note that "about 80 nm" is reasonably found to be close enough to the 100 nm size of Bergeron to share properties, particularly in light of the range in claim 16 from "about 30 to about 150 nanometers." See In re Peterson, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties").

Appellants contend that the "Examiner cannot simply shift the burden to Applicants by citing references that do not teach, mention, or even remotely suggest lipid-drug complexes with the claimed drug-releasing property and that disclose drug-encapsulating liposomes prepared by different methods than those used to prepare the currently claimed lipid-drug complex" (App. Br. 10).

We are not persuaded. It is the essence of Best that "[w]here, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product." In re Best, 562 F.2d at 1255 (emphasis added). In the instant case, the prior art products are identical in structural requirements to the product of claim 1, silent only with regard to the functional characteristic required by claim 1. As we have already noted, neither Appellants' Specification (FF 1, 6) nor Appellants

claim 1 require a particular process for forming the lipid-drug complex. Consequently, we agree with the Examiner that the burden of showing that the liposomes of Bergeron in view of Kirpotin fail to satisfy the functional requirement is properly placed upon Appellants. For this rejection, the proper comparison would be with the liposomes of Bergeron.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that the burden of showing whether Bergeron and Kirpotin's lipid-drug complex inherently satisfies the functional requirement of claim 1 that "at least one drug molecule substantially dissociates from the lipid-drug complex within a pH range from about pH 5.0 to about pH 5.5" is properly placed on Appellants.

SUMMARY

In summary, we affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as obvious over Kirpotin. Pursuant to 37 C.F.R. § 41.37(c)(1), we also affirm the rejection of claims 2, 3, 5, 7-9, and 15-17, as these claims were not argued separately.

We affirm the rejection of claim 6 under 35 U.S.C. § 103(a) as obvious over Kirpotin, Thibodeau, and Konigsberg.

We affirm the rejection of claim 1, 16 and 17 under 35 U.S.C. § 103(a) as obvious over Bergeron and Kirpotin. Pursuant to 37 C.F.R. § 41.37(c)(1), we also affirm the rejection of claims 2, 3, 5, 7-9, and 15, as these claims were not argued separately.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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